```
     (FILE 'USPAT' ENTERED AT 09:29:35 ON 20 JUN 1997)
L1           135 S GLUCAGON LIKE PEPTIDE OR GLUCAGON LIKE INSULINOTROPIC PE
PTI
L2          8694 S DIABET?
L3             9 S L1 (P) L2
L4           433 S TYPE I DIABETES OR IDDM
L5             1 S L4 (P) L1
=> logoff y
U.S. Patent & Trademark Office LOGOFF AT 09:48:30 ON 20 JUN 1997
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Set      Items   Description
S1       19742   TYPE(W)I(W)DIABETES OR IDDM
S2        2638   GLIP OR GLP
S3        2243   GLUCAGON(1N)LIKE(1N)PEPTIDE
S4          18   GLUCAGON(W)LIKE(W)INSULINOTROPIC(1N)PEPTIDE
S5        3477   S2 OR S3 OR S4
S6          14   S1 AND S5
S7           9   RD (unique items)
?

INT CONF
!


?LOGOFF
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7/7,K/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13174192 BIOSIS Number: 99174192
Insulin saving by GLP-1 in fasting normoglycaemic IDDM
Freyse E J; Knospe S; Becher T; El Hag O; Goke B; Fischer U
Inst. Diabetes "Gerhardt Katsch", Ernst-Moritz-Arndt-Univ., Greifswald, Germany
Diabetologia 39 (SUPPL. 1). 1996. A155.
Full Journal Title: 32nd Annual Meeting of the European Association for the Study of Diabetes, Vienna, Austria, September 1-5, 1996. Diabetologia
ISSN: 0012-186X
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 010 Ref. 180795

Insulin saving by GLP -1 in fasting normoglycaemic IDDM
Descriptors/Keywords: MEETING ABSTRACT; MEETING POSTER; DOG; GLUCAGON - LIKE PEPTIDE -1; NORMOGLYCEMIC; INSULIN-DEPENDENT DIABETES MELLITUS; ALANINE

7/7,K/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11844659 BIOSIS Number: 98444659
Glucagon-like peptide 1 (GLP-1) diminishes glycemic response to meals in C-peptide-positive type 1 diabetics and normal humans
Dupre J; Behme M T; Hramiak I M; McDonald T J; McFarlane P; Williamson M P
Univ. Western Ont., London, ON, Canada
Clinical and Investigative Medicine 18 (4 SUPPL.). 1995. B44.
Full Journal Title: Annual Meeting of the Canadian Society for Clinical Investigation and the Royal College of Physicians and Surgeons of Canada, Montreal, Quebec, Canada, September 13-17, 1995. Clinical and Investigative Medicine
ISSN: 0147-958X
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 047 Iss. 010 Ref. 176414

Glucagon - like peptide 1 (GLP -1) diminishes glycemic response to meals in C-peptide-positive type 1 diabetics and normal...
Descriptors/Keywords: MEETING ABSTRACT; GLUCAGON - LIKE PEPTIDE -1 7-36 AMIDE; ANTIDIABETIC-DRUG; HORMONE-DRUG; METABOLIC-DRUG; INSULIN; ANTIDIABETIC-DRUG; HORMONE-DRUG; METABOLIC-DRUG; PHARMACODYNAMICS; SUBCUTANEOUS INJECTION; ENDOCRINOLOGY; PANCREATIC POLYPEPTIDE; BODY MASS INDEX; TYPE - I DIABETES ; INSULIN-DEPENDENT DIABETES MELLITUS

7/7,K/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11781541 BIOSIS Number: 98381541
Glucagon-like peptide I reduces postprandial glycemic excursions in IDDM
Dupre J; Behme M T; Hramiak I M; McFarlane P; Williamson M P; Zabel P; McDonald T J
Univ. Hospital, 339 Windermere Rd., London N6A 5A5, Canada
Diabetes 44 (6). 1995. 626-630.
Full Journal Title: Diabetes
ISSN: 0012-1797
Language: ENGLISH
Print Number: Biological Abstracts Vol. 100 Iss. 005 Ref. 073379
Effects of human glucagon-like peptide I (GLP-I)(7-36)amide were examined in volunteers having insulin-dependent diabetes mellitus (EDDM) with residual C-peptide (CP) secretion (n = 8, 7 men and 1 woman; age, 31 +- 1.4 years; body mass index, 24.7 +- 0.7 kg/m-2; duration of diabetes, 3.2 +- 0.8 years; insulin dose, 0.41 +- 0.05 U cntdot kg-1 cntdot day-1; meal-stimulated CP, 1.0 +- 0.2 nmol/l (means t SE)). After a mixed meal (Sustacal, 30 kJ/kg body wt), intravenous injection of GLP-1, 1.2 pmol cntdot kg-1 cntdot min-1 through 120 min, virtually abolished increments of plasma glucose, CP, pancreatic polypeptide (PP), and glucagon concentrations, with no significant effect on plasma gastrin levels during the infusions. At reduced dosage (0.75 pmol cntdot kg-1 cntdot min-1), GLP-1 had lesser effects on plasma glucose and CP levels. On cessation of intravenous GLP-1 infusions after the meals, plasma glucose, CP, PP, and

glucagon concentrations rebounded toward control levels by 180 min, and the response of plasma gastrin was prolonged. These rebound responses are consistent with intestinal delivery of food retained in the stomach on escape from inhibition of gastric emptying by GLP-I. Infusion of 1.2 pmol cntdot kg-1 cntdot min-1), with 20 g glucose (10% dextrose in water) injected intravenously over 60 min enhanced plasma responses of immunoreactive CP; the mean incremental areas under concentration curves (0-60 min) increased sixfold, but the glycemic excursion was not affected. Thus, in CP-positive IDDM, pharmacological doses of GLP-I reduce glycemic excursions after meals by a mechanism(s) not dependent on stimulation of insulin secretion, presumably involving delayed gastric emptying. This effect of the peptide on blood glucose levels after meals may have therapeutic implications in both IDDM and non-insulin-dependent diabetes.

Glucagon - like peptide I reduces postprandial glycemic excursions in IDDM

Effects of human glucagon - like peptide I (GLP -I)(7-36)amide were examined in volunteers having insulin-dependent diabetes mellitus (EDDM) with...

... t SE)). After a mixed meal (Sustacal, 30 kJ/kg body wt), intravenous injection of GLP -1, 1.2 pmol cntdot kg-1 cntdot min-1 through 120 min, virtually abolished...

... during the infusions. At reduced dosage (0.75 pmol cntdot kg-1 cntdot min-1), GLP -1 had lesser effects on plasma glucose and CP levels. On cessation of intravenous GLP -1 infusions after the meals, plasma glucose, CP, PP, and glucagon concentrations rebounded toward control...

... delivery of food retained in the stomach on escape from inhibition of gastric emptying by GLP -I. Infusion of 1.2 pmol cntdot kg-1 cntdot min-1), with 20 g...

... 60 min) increased sixfold, but the glycemic excursion was not affected. Thus, in CP-positive IDDM , pharmacological doses of GLP -I reduce glycemic excursions after meals by a mechanism(s) not dependent on stimulation of...

... of the peptide on blood glucose levels after meals may have therapeutic implications in both IDDM and non-insulin-dependent diabetes.

Descriptors/Keywords: RESEARCH ARTICLE; HUMAN; GLUCAGON - LIKE PEPTIDE -1; ANTIDIABETIC-DRUG; BLOOD GLUCOSE LEVEL; C-PEPTIDE SECRETION; INSULIN-DEPENDENT DIABETES MELLITUS; NON-INSULIN...

7/7,K/4 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

9522086 BIOSIS Number: 94027086

ANTIDIABETOGENIC EFFECT OF GLUCAGON-LIKE PEPTIDE-1 7-36-AMIDE IN NORMAL SUBJECTS AND PATIENTS WITH DIABETES MELLITUS

GUTNIAK M; ORSKOV C; HOLST J J; AHREN B; EFENDIC S

KAROLINSKA INST., KAROLINSKA SJUKHUSET, BOX 60500, S-104 01 STOCKHOLM, SWEDEN.

N ENGL J MED 326 (20). 1992. 1316-1322. CODEN: NEJMA

Full Journal Title: New England Journal of Medicine

Language: ENGLISH

Background: Glucagon-like peptide-1 (7-36) amide (glucagon-like insulinotropic peptide, or GLIP) is a gastrointestinal peptide that potentiates the release of insulin in physiologic concentrations. Its effects in patients with diabetes mellitus are not known. Methods: We compared the effect of an infusion of GLIP that raised plasma concentrations of GLIP twofold with the effect of an infusion of slaine, on the meal-related release of insulin, glucagon, and somatostatin in eight normal subjects, nine obese patients with non-insulin-dependent diabetes mellitus (NIDDM), and eight patients with insulin-dependent diabetes mellitus (IDDM). The blood glucose concentrations in the patients with diabetes were controlled by a closed-loop insulin-infusion system (artificial pancreas) during the infusion of each agent, allowing measurement of the meal-related requirement for exogenous insulin. In the patients with IDDM, normoglycemic-clamp studies were performed during the infusions of GLIP and saline to determine the effect of GLIP on insulin sensitivity. Results: In the normal subjects, the infusion of GLIP significantly lowered the meal-related increases in the blood glucose concentration ($P < 0.01$) and the plasma concentrations of insulin and glucagon ($P < 0.05$ for both comparisons). The insulinogenic index (the ratio of insulin to glucose) increased almost 10-fold, indicating that GLIP

had an insulinotropic effect. In the patients with NIDDM, the infusion of GLIP reduced the mean (.+-. SE) calculated isoglycemic meal-related requirement for insulin from 17.4 .+-. 2.8 to 2.0 .+-. 0.5 U (P < 0.001), so that the integrated area under the curve for plasma free insulin was decreased (P < 0.05) in spite of the stimulation of insulin release. In the patients with IDDM, the GLIP infusion decreased the calculated isoglycemic meal-related insulin requirement from 9.4 .+-. 1.5 to 4.7 .+-. 1.4 U. The peptide decreased glucagon and somatostatin release in both groups of patients. In the normoglycemic-clamp studies in the patients with IDDM, the GLIP infusion significantly increased glucose fertilization (saline vs. GLIP, 7.2 .+-. 0.5 vs. 8.6 .+-. 0.4 mg per kilogram of body weight per minute; P < 0.01). Conclusion: GLIP has an antidiabetogenic effect, and it may therefore be useful in the treatment of patients with NIDDM.

ANTIDIABETOGENIC EFFECT OF GLUCAGON - LIKE PEPTIDE -1 7-36-AMIDE IN NORMAL SUBJECTS AND PATIENTS WITH DIABETES MELLITUS

Background: Glucagon - like peptide -1 (7-36) amide (glucagon - like insulinotropic peptide , or GLIP) is a gastrointestinal peptide that potentiates the release of insulin in physiologic concentrations. Its effects...

...with diabetes mellitus are not known. Methods: We compared the effect of an infusion of GLIP that raised plasma concentrations of GLIP twofold with the effect of an infusion of slaine, on the meal-related release of...

...with non-insulin-dependent diabetes mellitus (NIDDM), and eight patients with insulin-dependent diabetes mellitus (IDDM). The blood glucose concentrations in the patients with diabetes were controlled by a closed-loop...

... agent, allowing measurement of the meal-related requirement for exogenous insulin. In the patients with IDDM , normoglycemic-clamp studies were performed during the infusions of GLIP and saline to determine the effect of GLIP on insulin sensitivity. Results: In the normal subjects, the infusion of GLIP significantly lowered the meal-related increases in the blood glucose concentration (P < 0.01) and...
... The insulinogenic index (the ratio of insulin to glucose) increased almost 10-fold, indicating that GLIP had an insulinotropic effect. In the patients with NIDDM, the infusion of GLIP reduced the mean (.+-. SE) calculated isoglycemic meal-related requirement for insulin from 17.4 .+-. 2...

... P < 0.05) in spite of the stimulation of insulin release. In the patients with IDDM , the GLIP infusion decreased the calculated isoglycemic meal-related insulin requirement from 9.4 .+-. 1.5 to...

... release in both groups of patients. In the normoglycemic-clamp studies in the patients with IDDM , the GLIP infusion significantly increased glucose fertilization (saline vs. GLIP , 7.2 .+-. 0.5 vs. 8.6 .+-. 0.4 mg per kilogram of body weight per minute; P < 0.01). Conclusion: GLIP has an antidiabetogenic effect, and it may therefore be useful in the treatment of patients...

7/7,K/5 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

10258828 EMBASE No: 97069700

Subcutaneous glucagon-like peptide I combined with insulin normalizes postcibal glycemic excursions in IDDM

Dupre J.; Behme M.T.; Hramiak I.M.; McDonald T.J.
Canada

Diabetes Care (USA) , 1997, 20/3 (381-384) CODEN: DICAD ISSN: 0149-5992
DOCUMENT TYPE: Journal
LANGUAGES: English SUMMARY LANGUAGES: English
NUMBER OF REFERENCES: 9

OBJECTIVE - To determine whether a subcutaneous injection of truncated glucagon-like peptide I (tGLP-I)(7-36) amide that delays gastric emptying transiently can prevent postcibal hyperglycemia in IDDM without causing hypoglycemia when administered with insulin. RESEARCH DESIGN AND METHODS - The postcibal increase in plasma human pancreatic polypeptide (HPP) was used as a presumptive indicator of arrival of nutrient in the small intestine. Studies in seven normal human volunteers established the dose of tGLP-I that delayed the postcibal rise in HPP by 30 min. This dose was tested in six patients with IDDM with a range of residual endogenous insulin secretion. The patients received a standard liquid test meal with

or without subcutaneous tGLP-I and their usual dose of regular insulin before the meal. Blood samples collected at timed intervals were assayed for plasma concentrations of glucose, C-peptide (CP), immunoreactive insulin (IRI), HPP, and glucagon (GLN). RESULTS - In normal subjects after administration of tGLP-I, postcibal plasma glucose concentration at 20 min fell below fasting levels in a dose- dependent manner. At 10 and 20 min, transient increments in plasma CP and IRI, and decrements in GLN, occurred. Subsequently, through 60 min, the excursions of plasma HPP, CP, and IRI were negatively correlated to the dose of tGLP-I. In subjects with IDDM, the selected dose of tGLP-I given with insulin before the meal delayed the plasma HPP response for 30 min and confined excursions of plasma glucose within the range observed in normal subjects receiving saline injections, whereas administration of insulin with saline injections in IDDM was followed by supranormal increases of plasma glucose. In IDDM, this dose of subcutaneous tGLP-I had no effect on plasma CP, IRI, or GLN. CONCLUSIONS - In normal subjects, transient hypoglycemia after injections of tGLP-I with a meal was associated with transient stimulation of insulin secretion and inhibition of glucagon secretion. These actions together with delayed gastric emptying may account for the hypoglycenna, but other unidentified mechanisms cannot be excluded. In the subjects with IDDM, the selected relatively low dose of tGLP-I delayed excursions of plasma HPP as in normal subjects, but did not reduce the plasma glucose below the fasting level and had no effect on plasma CP, IRI, or GLN. However, injection of tGLP-I reduced the postcibal glycemic excursion and confined it within the normal range. Thus, in IDDM, a pharmacological dose of subcutaneous tGLP-I that presumably delays gastric emptying by similar30 min can normalize glycemic excursions after a meal when given in combination with insulin. Because this cannot be achieved with regular insulin alone without risk of hypoglycemia, this combination of glucoregulatory peptides has therapeutic potential in insulin-requiring diabetes.

Subcutaneous glucagon - like peptide I combined with insulin normalizes postcibal glycemic excursions in IDDM
OBJECTIVE - To determine whether a subcutaneous injection of truncated glucagon - like peptide I (tGLP-I)(7-36) amide that delays gastric emptying transiently can prevent postcibal hyperglycemia in IDDM without causing hypoglycemia when administered with insulin. RESEARCH DESIGN AND METHODS - The postcibal increase in...

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... I reduced the postcibal glycemic excursion and confined it within the normal range. Thus, in IDDM , a pharmacological dose of subcutaneous tGLP-I that presumably delays gastric emptying by similar30 min...
DRUG DESCRIPTORS:
* glucagon like peptide 1 (7-36) amide--clinical trial--ct; * glucagon like peptide 1 (7-36) amide--drug administration--ad; * glucagon like peptide 1 (7-36) amide--drug combination--cb; * glucagon like peptide 1 (7-36) amide--drug dose--do; * glucagon like peptide 1 (7-36) amide--drug therapy--dt; *insulin--clinical trial--ct; *insulin --drug combination--cb...

7/7,K/6 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

10236441 EMBASE No: 97039842
Signal transduction of PACAP and GLP-1 in pancreatic beta cells
Leech C.A.; Holz G.G.; Habener J.F.; Makhlouf G.M.; DiCicco-Bloom E.; Yada T.; Bataille D.
C.A. Leech, Laboratory Molecular Endocrinology, Massachusetts General

Hospital, Harvard Medical School, Boston, MA 02114 USA
Annals of the New York Academy of Sciences (USA) , 1996, 805/- (81-93)
CODEN: ANYAA ISSN: 0077-8923
DOCUMENT TYPE: Journal
LANGUAGES: English SUMMARY LANGUAGES: English
NUMBER OF REFERENCES: 44

PACAP and GLP-1 depolarize pancreatic beta cells and stimulate insulin secretion in the presence of glucose. Depolarization occurs through at least two distinct mechanisms: (1) closure of ATP-sensitive K+ channels, and (2) activation of nonselective cation channels (NSCCs). Under physiological conditions the NSCCs carry a predominantly Na+-dependent current. The current may also have a Ca2+ component, but this remains to be determined. Acting together, these two signaling systems reinforce each other and serve to promote membrane depolarization, a rise of (Ca2+)(i), and exocytosis of insulin-containing secretory granules. The NSCCs in beta cells are dually regulated by intracellular cAMP and (Ca2+)(i). In view of this dual regulation, it appears likely that NSCC channel activation results from signaling events occurring not only at the plasma membrane (gating of channels by cAMP; protein kinase A-mediated phosphorylation of channels) but also at intracellular sites (mobilization of calcium stores by an as yet to be determined process). It is noteworthy that activation of NSCCs has also been reported following stimulation of beta-cells with maitotoxin, or after depletion of intracellular Ca2+ stores. Therefore, the possibility arises that PACAP, GLP-1, and maitotoxin all act on the same types of ion channels in these cells, and that these channels are sensitive to alterations in the content of intracellular calcium. FIGURE 6 summarizes our current knowledge concerning the properties of the PACAP and GLP-1 signaling systems as they pertain to the regulation of NSCCs and intracellular calcium homeostasis in the beta cell. Given that PACAP and GLP-1 are proven to be exceptionally potent insulin secretagogues, it is of considerable interest to determine their usefulness as blood glucose-lowering agents. Initial evaluations of the therapeutic effectiveness of GLP-1 indicate a role for this peptide in the treatment of NIDDM, and also possibly insulin-dependent diabetes mellitus (IDDM). A very attractive feature of such a strategy is the demonstrated lack of hypoglycemic side effects attendant to administration of GLP-1 to diabetic subjects. These observations reinforce the notion that peptides of the PACAP/glucagon/VIP family represent important pharmacological tools for use in experimental therapeutics.

Signal transduction of PACAP and GLP -1 in pancreatic beta cells
PACAP and GLP -1 depolarize pancreatic beta cells and stimulate insulin secretion in the presence of glucose. Depolarization...

... with maitotoxin, or after depletion of intracellular Ca2+ stores. Therefore, the possibility arises that PACAP, GLP -1, and maitotoxin all act on the same types of ion channels in these cells...

... intracellular calcium. FIGURE 6 summarizes our current knowledge concerning the properties of the PACAP and GLP -1 signaling systems as they pertain to the regulation of NSCCs and intracellular calcium homeostasis in the beta cell. Given that PACAP and GLP -1 are proven to be exceptionally potent insulin secretagogues, it is of considerable interest to determine their usefulness as blood glucose-lowering agents. Initial evaluations of the therapeutic effectiveness of GLP -1 indicate a role for this peptide in the treatment of NIDDM, and also possibly insulin-dependent diabetes mellitus (IDDM). A very attractive feature of such a strategy is the demonstrated lack of hypoglycemic side effects attendant to administration of GLP -1 to diabetic subjects. These observations reinforce the notion that peptides of the PACAP/glucagon...
DRUG DESCRIPTORS:
*hypophysis adenylate cyclase activating polypeptide; * glucagon like peptide 1

CAS REGISTRY NO.: 137061-48-4 (hypophysis adenylate cyclase activating polypeptide); 89750-14-1 (glucagon like peptide 1); 9004-10-8 (insulin); 50-99-7...

7/7,K/7 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

10136422 EMBASE No: 96316224
Human studies with glucagon-like-peptide-1: Potential of the gut hormone for clinical use
Byrne M.M.; Goke B.

Clinical Research Unit, Department of Internal Medicine, Philipps University, Marburg Germany
Diabetic Medicine (United Kingdom) , 1996, 13/10 (854-860) CODEN: DIMEE ISSN: 0742-3071
LANGUAGES: English SUMMARY LANGUAGES: English
So far, a wealth of data originating from in vitro or animal experiments has been collected supporting the concept that the gut hormone, glucagon-like peptide-1 (GLP-1) may serve as a model molecule for the design of a new drug for the treatment of diabetes mellitus. This is supported by observations that GLP-1 has potent insulinotropic action in patients with non-insulin-dependent diabetes mellitus (NIDDM). It enhances beta-cell sensitivity to glucose stimulated insulin secretion. GLP-1 may also have a role in the treatment of impaired glucose tolerance, where the beta-cell is already insensitive to changes in plasma glucose concentrations. It may, as has previously been shown in animal models of 'prediabetes', delay the progressive decline in glucose tolerance to NIDDM. The glucose-dependent action of this peptide is an important feature in the treatment of NIDDM as it will protect against hypoglycaemic reactions, the most serious acute side-effect of antidiabetic therapy. Glucose utilization may be enhanced which would improve metabolic control in both NIDDM and IDDM. A glucagon lowering effect will further enhance metabolic control. This article reviews current experiences of the effects of GLP-1 in human studies. It points out the outcomes and limitations of previous trials and discusses future directions for the investigation of its potential use as a new agent in diabetes treatment.

Human studies with glucagon - like - peptide -1: Potential of the gut hormone for clinical use
... in vitro or animal experiments has been collected supporting the concept that the gut hormone, glucagon - like peptide -1 (GLP -1) may serve as a model molecule for the design of a new drug for the treatment of diabetes mellitus. This is supported by observations that GLP -1 has potent insulinotropic action in patients with non-insulin-dependent diabetes mellitus (NIDDM). It enhances beta-cell sensitivity to glucose stimulated insulin secretion. GLP -1 may also have a role in the treatment of impaired glucose tolerance, where the...

... therapy. Glucose utilization may be enhanced which would improve metabolic control in both NIDDM and IDDM . A glucagon lowering effect will further enhance metabolic control. This article reviews current experiences of the effects of GLP -1 in human studies. It points out the outcomes and limitations of previous trials and...
DRUG DESCRIPTORS:
* glucagon like peptide 1--pharmacology--pd; * glucagon like peptide 1--drug therapy--dt; * glucagon like peptide 1--drug administration--ad

7/7,K/8 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07389710 92228024
Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus [see comments]
Gutniak M; Orskov C; Holst JJ; Ahren B; Efendic S
Department of Endocrinology, Karolinska Institute, Stockholm, Sweden.
N Engl J Med (UNITED STATES) May 14 1992, 326 (20) p1316-22, ISSN 0028-4793 Journal Code: NOW
Comment in N Engl J Med 1992 May 14;326(20):1352-3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND. Glucagon-like peptide-1 (7-36) amide (glucagon-like insulinotropic peptide, or GLIP) is a gastrointestinal peptide that potentiates the release of insulin in physiologic concentrations. Its effects in patients with diabetes mellitus are not known. METHODS. We compared the effect of an infusion of GLIP that raised plasma concentrations of GLIP twofold with the effect of an infusion of saline, on the meal-related release of insulin, glucagon, and somatostatin in eight normal subjects, nine obese patients with non-insulin-dependent diabetes mellitus (NIDDM), and eight patients with insulin-dependent diabetes mellitus (IDDM). The blood glucose concentrations in the patients with diabetes were controlled by a closed-loop insulin-infusion system (artificial pancreas) during the infusion of each agent, allowing measurement of the meal-related requirement for exogenous insulin. In the patients with IDDM, normoglycemic-clamp studies were performed during the infusions of GLIP and saline to determine the effect of GLIP on insulin

sensitivity. RESULTS. In the normal subjects, the infusion of GLIP significantly lowered the meal-related increases in the blood glucose concentration (P less than 0.01) and the plasma concentrations of insulin and glucagon (P less than 0.05 for both comparisons). The insulinogenic index (the ratio of insulin to glucose) increased almost 10-fold, indicating that GLIP had an insulinotropic effect. In the patients with NIDDM, the infusion of GLIP reduced the mean (+/- SE) calculated isoglycemic meal-related requirement for insulin from 17.4 +/- 2.8 to 2.0 +/- 0.5 U (P less than 0.001), so that the integrated area under the curve for plasma free insulin was decreased (P less than 0.05) in spite of the stimulation of insulin release. In the patients with IDDM, the GLIP infusion decreased the calculated isoglycemic meal-related insulin requirement from 9.4 +/- 1.5 to 4.7 +/- 1.4 U. The peptide decreased glucagon and somatostatin release in both groups of patients. In the normoglycemic-clamp studies in the patients with IDDM, the GLIP infusion significantly increased glucose utilization (saline vs. GLIP, 7.2 +/- 0.5 vs. 8.6 +/- 0.4 mg per kilogram of body weight per minute; P less than 0.01). CONCLUSIONS. GLIP has an antidiabetogenic effect, and it may therefore be useful in the treatment of patients with NIDDM.

Antidiabetogenic effect of glucagon - like peptide -1 (7-36)amide in normal subjects and patients with diabetes mellitus [see comments]
BACKGROUND. Glucagon - like peptide -1 (7-36) amide (glucagon - like insulinotropic peptide , or GLIP) is a gastrointestinal peptide that potentiates the release of insulin in physiologic concentrations. Its effects...

...with diabetes mellitus are not known. METHODS. We compared the effect of an infusion of GLIP that raised plasma concentrations of GLIP twofold with the effect of an infusion of saline, on the meal-related release of...

...with non-insulin-dependent diabetes mellitus (NIDDM), and eight patients with insulin-dependent diabetes mellitus (IDDM). The blood glucose concentrations in the patients with diabetes were controlled by a closed-loop...

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... The insulinogenic index (the ratio of insulin to glucose) increased almost 10-fold, indicating that GLIP had an insulinotropic effect. In the patients with NIDDM, the infusion of GLIP reduced the mean (+/- SE) calculated isoglycemic meal-related requirement for insulin from 17.4 +/- 2 ...

... than 0.05) in spite of the stimulation of insulin release. In the patients with IDDM , the GLIP infusion decreased the calculated isoglycemic meal-related insulin requirement from 9.4 +/- 1.5 to...

... release in both groups of patients. In the normoglycemic-clamp studies in the patients with IDDM , the GLIP infusion significantly increased glucose utilization (saline vs. GLIP , 7.2 +/- 0.5 vs. 8.6 +/- 0.4 mg per kilogram of body weight per minute; P less than 0.01). CONCLUSIONS. GLIP has an antidiabetogenic effect, and it may therefore be useful in the treatment of patients...
Chemical Name: Blood Glucose; (C-Peptide; (Peptide Fragments; (Peptides ; (Insulin; (glucagon - like peptide I (7-36)amide; (Somatostatin; (Glucagon

7/7,K/9 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI

010513740 **Image available**
WPI Accession No: 96-010691/199601
Treating insulin-requiring diabetes with glucagon-like peptide or derivs. - opt. together with insulin, provides improved control of blood glucose levels
Patent Assignee: LONDON HEALTH ASSOC (LONH-N)
Inventor: DUPRE J
Number of Countries: 018 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
WO 9531214	A1	19951123	WO 95CA287	A	19950512	A61K-038/26	199601 B
AU 9524044	A	19951205	AU 9524044	A	19950512	A61K-038/26	199620
EP 762890	A1	19970319	EP 95917874	A	19950512	A61K-038/26	199716
			WO 95CA287	A	19950512		

Priority Applications (No Kind Date): GB 949496 A 19940512
Cited Patents: 2. journal ref.; WO 9111457; WO 9325579
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
WO 9531214	A1	E	29			
AU 9524044	A			Based on		WO 9531214
EP 762890	A1	E		Based on		WO 9531214

Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

Abstract (Basic): WO 9531214 A

Insulin-requiring diabetes is treated by admin of (a) insulin and (b) glucagon-like peptide 1 (7-37) (IIa), glucagon-like peptide 1 (7-36) amide (IIb), or an analogue or fragment of (IIa) or (IIb). Also new is the treatment of type I diabetes with these peptides alone without using insulin.

USE - The method is used in human medicine for the treatment of types I or II diabetes. The use of (IIa)/(IIb) alone may be suitable for treating some cases of type I, partic. in remission phase subjects. The peptides may be given orally, nasally or parenterally.

ADVANTAGE - The use of (IIa)/(IIb), opt. in (synergistic) combination with oral hypoglycaemics, is already known for treatment of non-insulin dependent diabetes. It is now found, that these peptides improve control of glycaemia in patients requiring insulin. When administered before a meal, they delay the increase in blood glucose levels by inhibiting emptying of the stomach (insulin secretion is not affected) and thus, should be effective even in patients with no residual insulin-secreting capacity. The use of the peptides may make it possible to reduce the overall insulin dose.

Dwg.1/6

Derwent Class: B04
International Patent Class (Main): A61K-038/26
International Patent Class (Additional): A61K-038/26; A61K-038-28

Treating insulin-requiring diabetes with glucagon - like peptide or derivs...

...Abstract (Basic): Insulin-requiring diabetes is treated by admin of (a) insulin and (b) glucagon - like peptide 1 (7-37) (IIa), glucagon - like peptide 1 (7-36) amide (IIb), or an analogue or fragment of (IIa) or (IIb). Also new is the treatment of type I diabetes with these peptides alone without using insulin...

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